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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/167,351 10/07/98 HAAF

K 514413-3563

EXAMINER

HM22/1205

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NEW YORK NY 10151

ART UNIT PAPER NUMBER

DATE MAILED: 7

12/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
09/167,351

Applicant

Haaf et al.

Examiner  
Grac Hsu, Ph.D.

Group Art Unit  
1627



☒ Responsive to communication(s) filed on Sep 5, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 2-9 and 16 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 2-9 and 16 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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### DETAILED ACTION

1. An Amendment Under 37 C.F.R. 1.111 and A Petition Under 37 C.F.R. 1.136 received September 5, 2000 was entered as Paper No. 8.

#### *Status of Claims*

2. Claims 2-9 and claim 16 (newly added) are pending and under examination in the current application.
3. Claims 1 and 10-15 are cancelled as per applicants September 5, 2000 request.

#### *Response to the September 5, 2000 Amendment Under 37 C.F.R. 1.111.*

4. For the record, it is noted that applicants': [1] have received a February 29, 2000 action on the merits for the originally claimed invention; and that [2] arguments as set forth in applicants' September 5, 2000 Amendment have been directed to the claims **as amended** and not to the claims as originally presented for examination in the February 29, 2000 Office Action.
5. Applicants' arguments filed in the September 5, 2000 Amendment have been fully considered and discussed below, under each corresponding section heading.
6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### *Withdrawn Objection(s) and/or Rejection(s)*

7. The objection of claims 1-9 due to improper language use of idiomatic English and grammatical errors are withdrawn in favor of new rejections below.

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8. The objection to the disclosure for failure to identify a reference to the prior application as the first sentence of the specification is withdrawn in light of applicants amendments.

9. The rejection of claims 1 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101 is withdrawn in light of applicants' cancellation of claim 1 and new claim 16.

***Outstanding Objection(s) and Rejection(s)***

10. The following rejections are maintained for reasons of record and are addressed together after paragraph 12.

11. The rejection of claims 2-9 and 16 (formerly directed to claims 1-9) under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01 are maintained for the following reasons of record.

12. The rejection of claims 2-9 and 16 (formerly directed to claims 1-9) under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are maintained for the following reasons of record.

**In the September 5, 2000 Response, applicants assert that:**

- [1] the cancellation of claim 1 in favor of claim 16, a newly re-drafted version of claim 1 removes all grammatical objections, 112, 2nd vague and indefinite and antecedent basis issues and that the terms used in the claims convey a clear

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meaning to a practitioner in the art and that the claim language precisely defines the claimed invention in terminology conventionally used in the art;

**In response, it is the position of the Examiner that:**

[1] applicants' arguments have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record.

[a] without any further reiteration, note that the arguments set forth in the previous office action are still applicable for the following reasons:

[1] while the Examiner can appreciate that the claimed invention is directed to a process for preparing phosphorus chemical compounds via the use of solid support resins or even to formation of combinatorial methods as suggested by applicants

(as defined in the instant specification by clearly understood chemical structure illustrated by Scheme 1 (see, instant specification on page 30 and pages 46-49), Scheme 2 (see, instant specification on page 35); and by the Examples as set forth on pages 37-46);

[2] the claim language of either redrafted claims 16 (or original claim 1) and 2-9 are nevertheless **confusing to any** reader, because, applicants are trying to explain successive chemical transformations or modifications to a reaction sequence via the use of identical words or multiple variables that reappear as the same term(s) in successive steps in trying to define the steps of the claimed process.

[3] For example, in reaction step (a) the term:

"[resin-polymer]-[linker-Z-E1-S1]<sub>n</sub> appears with each of the elements of the aforementioned terms defined in a passage that follows it.

However, it remains unclear exactly how the "linker" term is attached to the resin polymer, and each of the respective elements Z, E1 and S1 to each other (i.e., what are the exact chemical bond

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associations between the linker and the resin and with each of the other elements to each other and the linker resin component?)

In comparison, when Scheme 1 is examined the inter-bond associations between each of the aforementioned elements is understood readily (i.e., e.g., the linker is a para-iodo benzyl carboxylic acid and it is attached to the resin via its carboxyl group end and every subsequent chemical transformation after reaction with the respective palladium catalyst occurs on the phosphinic acid moiety end of the core structure complex to form each of the respective components of a library, etc.)

(The Examiner respectfully maintains that the claim language would be unclear even to an ordinary artisan, who would understand the claimed invention, if more clearly, expressed as in terms of chemical structures as shown in Scheme I, II and Examples set forth in the instant specification)

- [c] In light of the foregoing, applicants amendments to the claims have failed to define the metes and bounds of the aforementioned claims cannot be determined as the specification, claims and the art do not recognize a defined set of compounds that define the generic terms of the claims.

**In light of the foregoing, the above-identified rejections are maintained.**

13. The rejection of claims 1-9 under 35 U.S.C. § 103 (a) as being unpatentable over Schwabacher et al. (Synthesis, 1992, 1255-1260) in combination with Boyd et al. (Tetrahedron Lett., 1998, Vol. 37, No. 10, 1647-1650) are maintained for the following reasons of record.

Schwabacher et al. teaches: [1] a method for the preparation of series of phosphinic acids and its corresponding derivatives, such as methyl esters of monoarylphosphinic acids, symmetrical and unsymmetrical diarylphosphinates, etc. that may be difficult to prepare by other routes; [2] which involves palladium catalyzed coupling of alkyl (aryl, etc.) iodides with methyl (or other

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substituted) phosphinate(s); [3] that such a method is compatible with various functional groups; that such derivatization or functional group manipulations may be achieved via conventionally known reaction chemistry (many example are given in this reference: for example phosphinic esters are generally prepared by esterification of the phosphinic acids with different reagents, such as trialkyl phosphite, by alcoholysis of an aryl or alkylidichlorophosphine or by Raney nickel reduction of a phosphothioate, aryl derivatives may be derived by organonmetallic reagents, such as Grignard reagent or aluminum trichloride, alkylphosphinic acids may be derived from phosphinic acid by radical addition to alkenes or from addition of phosphinic acid to a ketone or imine, etc., [4] wherein, phosphorus nucleophiles compatible with the process include: esters of alkyl and phenyl phosphinic acids, alkyl phenyl phosphine oxides, triphenyl phosphine and phosphonate esters; proceeds in reasonable yield despite thermal and hydrolytic sensitivity of methyl phosphinate; and [5] and that such compounds are useful as herbicide intermediates.

In view of the above, Schwabacher et al. *differs* from the claimed invention in that it *does not teach* [1] the formation of phosphinic acid compounds and its derivatives **on a solid support resin**; wherein [2] an organic starting material intermediate, such as an alkyl or aryl iodide is first anchored to the solid support resin, and [3] followed by the addition of the phosphorus containing intermediate leading to the formation of phosphonic acids and its corresponding derivatives..

However, Boyd teaches [1] the use of a resin for the multiple phase synthesis of phosphinic acid containing products on a resin.

Boyd et al. teaches: [1] the “first report of direct incorporation of phosphinic containing entities into a resin”; [2] that relates to multiple solid phase synthesis of aminophosphinic acids based on solid phase methodologies; wherein [3] an organic starting material, such as an aryl or an alkyl imine is resin bound forming an organic resin bound intermediate; [4] that resin bound intermediate is reacted with a phosphinate intermediate, BTSP ( obtained by heating hexamethyldisilazane with ammonium phosphinate under inert atmosphere) which results in the resin bound 1-aminophosphinic acids (see, scheme 1, p. 1648) in which a nucleophilic addition and coupling results; [5] leading to the overall outcome of the synthetic strategy is the generation of a new phosphorus carbon bond by the addition of coupling reagent, BTSP, to resin bound aryl or alkylimines under very mild conditions; [6] to assess the purity and synthetic efficiency of this methodology, the formed phosphinic acid derivatives were selectively cleaved from the resin (using an acid hydrolysis) and isolated after standard workup procedures; [7] the above-identified method results in the high yield synthesis of a series of aliphatic and aromatic 1-aminophosphinic acid derivatives (see, Table I on p. 1649); [8] the main advantage of this solid phase methodology is that highly pure products can conveniently be prepared on a small scale in multiple reaction vessels; and [9] that such resin bound phosphino amino-acids and derivatives are (a) ripe for exploitation in the preparation of unique peptidomimetic combinatorial libraries; (b) modulate enzyme inhibitors, including therapeutic an angiotensin-converting enzyme (ACE), HIV protease and stromelysin-1 (MMP-3) inhibitor; (c ) are suitable for further studies and potential incorporation into unique combinatorial chemical libraries that can be screened for potential



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biological activities; and (d) that novel synthetic procedures enable rapid preparation of structurally diverse aminophosphinic acid analogues of considerable use and interest.

A person of ordinary skill in the art would have been motivated to develop a method for the preparation of substituted phosphinic acids and its derivatives that may be difficult to make by other routes which involves palladium catalyzed coupling of aryl iodides with methyl phosphinate; because such compounds are useful as herbicide intermediates as taught by Schwabacher et al. and are ripe for exploitation in the preparation of unique peptidomimetic combinatorial libraries as such compounds have been shown to modulate enzyme inhibitors, including therapeutic an angiotensin-converting enzyme (ACE), HIV protease and stromelysin-1 (MMP-3) inhibitor and may have potential for incorporation into unique combinatorial chemical libraries that can be screened for potential biological activities and that novel synthetic procedures enable rapid preparation of structurally diverse aminophosphinic acid analogues of considerable use and interest as taught by Boyd et al.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success such phosphinic acids and its corresponding derivatives because [1] Schwabacher et al. teaches a method for the preparation of methyl esters of monoarylphosphinic acids, symmetrical and unsymmetrical diarylphosphinates and their derivatives involving a palladium catalyzed coupling of alkyl, aryl, etc. iodides with phosphinates substituted with different substituent groups; and [2] Boyd et al. teaches: the "first report of direct incorporation of phosphinic containing entities into a resin" that relates to multiple solid phase synthesis of

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aminophosphinic acids based on solid phase methodologies which results in the resin bound 1-aminophosphinic acids or such phosphinic acid compounds cleaved from those solid supports.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Schwabacher et al. with the teachings of Boyd et al. to phosphine acids and its derivatives on solid support resins via a palladium catalyzed coupling reaction on a resin.

**In the September 5, 2000 Response, applicants assert that:**

- [1] the burden of establishing a prima facie case of obviousness has not been met because there is no suggestion or motivation to combine the references, in that:
  - [a] Schwabacher does not teach the claimed invention for reasons cited in the February 29, 2000 Office Action; and
  - [b] Boyd does not correct the "deficiencies of the Schwabacher reference as it does not teach solid phase synthesis for the compounds of the claimed invention and teaches a different reaction."
  - [c] Schwabacher would lead an ordinary artisan away from combining the Schwabacher and Boyd references, because Schwabacher teaches the use of "trimethylsilyl and tributylstannyl esters of hypophosphorus acid lead to only trace quantities of the desired phosphinates. . ." and Boyd teaches the use of bis(trimethylphosphinate) in the reaction forming 1-aminophosphinic acid.

**In response, it is the position of the Examiner that:**

- [1] Applicants' arguments have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record and are still applicable.;
- [2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed

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invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all three references relate to methods that:

- [a] in general involve [1] drug addiction, wherein it is conventionally known in the art that the term drug is defined as "something . . . often an illegal substance that causes addiction, habituation or a marked change in consciousness (see, Webster's dictionary, page 355)"; [2] nicotine as defined by Webster's dictionary is "a poisonous alkaloid  $C_{10}H_{14}N_2$ , that is the chief active principle of tobacco (see, Webster's dictionary, page 783)";

and in light of the above, more specifically:

- [a] Schwabacher et al. teaches a method for the preparation of series of phosphinic acids and its corresponding derivatives, such as methyl esters of monoarylphosphinic acids, symmetrical and unsymmetrical diarylphosphinates, etc. that may be difficult to prepare by other routes that reads on the claimed invention;
- [b] Boyd et al. was cited to illustrate that the synthesis of phosphinic acid derivatives as taught by Schwabacher et al. can be synthesized on solid supports if a known reaction chemistry has been mapped out; and

an ordinary artisan would not be lead away from combining the Schwabacher and Boyd references, Boyd teaches the use of bis(trimethylsilyl)phosphines (see, Scheme 1 of Boyd, step 2 on page 1648) and not bis(trimethylsilyl)phosphinates as taught by Schwabacher et al.

**In light of the above, the rejection is maintained for reasons of record.**

#### *New Rejections*

#### *Claim Rejections - 35 USC § 112*

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 2-9 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

[1] a process for the preparation of specific phosphorous containing compounds of the claimed invention as defined in the instant specification *most clearly* by:

[a] Scheme 1 (see, instant specification on page 30 and pages 46-49),

[b] Scheme 2 (see, instant specification on page 35); and

[c] by the Examples as set forth on pages 37-46; and

[2] the following specific reactants, reagents components, resins, etc. that are part of the chemical reaction as identified in the schemes and examples above:

wherein for the claimed invention:

[d] a resin is identified as formed from PS-Wang-OH;

[e] a linker is identified HCO<sub>2</sub>-paraphenyl-iodide

[f] the 5 specific classes of phosphinic derivative formed

[g] with specifically defined substituent groups (i.e., such that substituents attached to individual functional groups are clearly identified)

[h] specifically defined palladium catalysts, such as bis(triphenylphosphae)palladium(II) dichloride with hypophosphoric acid and triethyl orthoformate

[I] wherein for each of the aforementioned components, the specific substituents that each component are substituted with are defined by the substituent groups defined in the specification

*but the specification does not* reasonably provide enablement for a method for the preparation of *all* phosphorus compound derivatives that are potentially suggested by claim 2-9 and 16, using *all* linkers, *all* reactants with *all* potential types of functional group substitution patterns on each of

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those reactants, on *all* resins as means to effectuate the syntheses of the desired products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Factors considered in making such determinations are set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). As discussed below, those factors include, but are not limited to, the: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) level of one of ordinary skill; (5) level of predictability in the art; (6) amount of direction provided by the inventor; (7) existence of working examples; and (8) quantity of experimentation needed to make or use the invention cased on the disclosure content.

In the present case, [1] the breadth of the claims is directed to a process for the preparation of chemical compounds of formula (I). However, the examples in the specification as identified above teach only the synthesis of specific classes of compounds as indicated in the specification in Scheme 1 (see, instant specification on page 30 and pages 46-49), Scheme 2 (see, instant specification on page 35); and by the Examples as set forth on pages 37-46 to yield positive or negative results; [2] the nature of the invention cannot be determined in light of the foregoing and without knowing the specific compound classes to be prepared by a method of the claimed invention; [3] and [5] the state of the art and the level of predictability in the art cannot be predicted with any certainty what specific compound classes could be prepared by the claimed method and are likely to provide productive results beyond those compounds synthesized as demonstrated by Schemes 1 and 2 and Examples as taught in the instant specification; [4] and [6]

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the inventor provides no guidance beyond the aforementioned Examples taught in the specification. As a result one of ordinary skill in the art could not predict what other types of compounds could effectively be synthesized via methods of the claimed invention, other than those by taught by Schemes 1 and 2 and Examples in the instant specification; and [7] and [8] while the existence of working examples are limited to specification by Schemes 1 and 2 Examples, an indeterminate quantity of experimentation would be necessary to determine all potential test compounds to be screened by using the methods of the claimed invention.

In light of the preceding discussion, one skilled in the art *could not practice* the claimed invention *without undue experimentation*, as claims 1 and 6-7 fail to correlate reasonably with either the enabling disclosure of the specification and the claims.

#### *Status of Claims*

16. No claims are allowed in the above-identified application.

#### *Conclusion*

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Grace C. Hsu, Ph.D., J.D. whose telephone number is (703) 308-7005. The Examiner may be reached during normal business hours, Monday through Friday from 8:30 am to 6:00 pm (EST). A message may be left on the Examiner's voice mail.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jyothosna Venkat, Ph.D., may be reached at (703) 308-2439. The fax number assigned to Group 1627 is (703) 305-4242. Any inquiry of a general nature or relating to the status of this

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application should be directed to the Group 1627 receptionist whose telephone number is (703) 308-0196.

Grace C. Hsu, Ph.D.

December 4, 2000

  
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